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(71) Applicant
Pacific Chemical Co Ltd

(Incorporated in the Republic of Korea)

181 Hankang-Ro 2-Ka, Yongsan-Ku, Seoul, Republic of Korea

(72) Inventors
Sang Hoon Han
Woo Young Lee
Byeung Gon Lee
Jung Ju Kim
Jong Weon Ahn

(74) Agent and/or Address for Service
J Miller & Co
34 Bedford Row, Holborn, London, WC1R 4JH, United Kingdom

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(54) Skin whitening agents formulated as patches

(57) Skin whitening agents with tyrosinase inhibiting activity are administered percutaneously using patch formulations. Patches are typically in form of a covering layer, a reservoir layer containing the active compound, enhancers, stabilisers etc. and a removable protective layer. Active compound is ascorbic acid, kojic acid or hydroquinone etc.

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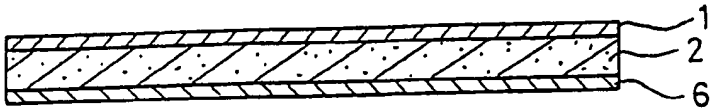
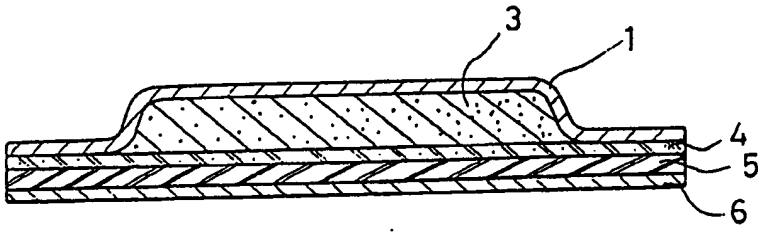
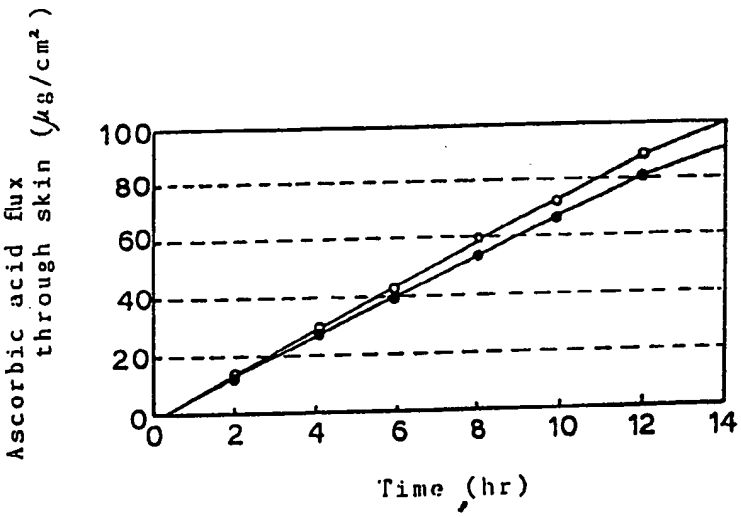


FIG, 1



FIG, 2



FIG, 3

SKIN PATCHES

The present invention relates to a new formulation form of cosmetic materials for whitening skin and more particularly, to patches for percutaneous administration of skin-whitening materials which comprise one or more skin-whitening materials having tyrosinase-inhibiting activity as an active compound and release the active compounds on the skin over a prolonged period.

In general, various factors participate in blackening of skin. Of the factors, a formation of melanin, a black pigment in a living body, by an action of tyrosinase on tyrosine when the skin is exposed to sun-light plays a key role in the skin blackening.

So far, cosmetic compositions incorporated with active compounds having tyrosinase-inhibiting activity such as ascorbic acid and its derivatives, kojic acid and its derivatives, N-glycose amines or hydroquinone and its derivatives have been employed for treating a blackening of skin or a freckled face. However, these conventional cosmetic compositions for whitening skin have several problems. For example, ascorbic acid, the most commonly

employed active compound, is labile in aqueous medium and is easily oxidized to dehydroascorbic acid by contact with air. Further, it undergoes browning during a long-term storage.

Many attempts for improving the stability of ascorbic acid have been made. For example, Japanese Unexamined Patent Publication No. Phyung 1-283208 discloses a method for adding phosphate to ascorbic acid followed by a modification by magnesium salts. Japanese Unexamined Patent Publication Nos. Phyung 1-228977, 1-228978 and 1-228989 teach methods for esterifying ascorbic acid with fatty acids such as stearic or palmitic acids.

These methods can improve the stability of ascorbic acid to some extent. However, they cannot provide a satisfactory skin-whitening effect due to inherent instability of ascorbic acid in aqueous medium, low solubility in cosmetic bases and low absorption into the skin.

Further, Japanese Unexamined Patent Publication No. Sho 64-79105 proposes incorporation of ascorbic acid into a facial pack. But, the skin-whitening effect which can be attained by the form of facial pack is unsatisfactory.

Besides, attempts have been made to whiten the skin by orally administering active compounds with skin-whitening property. However, this oral administration is an unproper method since the active compounds administered orally are metabolized in liver before they arrive and exhibit their activity at the desired locus and therefore one cannot administer high effective doses of active compounds.

Thus, there remains a need to provide a new form of

formulation which renders an administration of high effective doses of skin-whitening materials in a prolonged period without causing any irritation to skin.

Besides, pharmaceutical researchers have provided medicinal patches for transdermally delivering large doses of drugs over a prolonged period. For example, USP 4,615,699 to Gale et al. discloses a transdermal delivery system for delivering nitroglycerin, an active vasodilator, at high transdermal fluxes. USP 4,698,062 to Gale et al. teaches a medical device for pulsatile transdermal delivery of biologically active agents. USP 4,738,670 discloses antiinflammatory medicinal plasters comprising a covering layer, a reservoir layer and a detachable protective layer.

However, all of these patents relate to patches for medical purposes and are designed to transdermally deliver drugs such as antiinflammatory or vasodilating agents. Thus, the present invention to the first time provide a patch-form formulation of skin-whitening materials.

The present invention provides a patch for percutaneously administering skin-whitening materials having tyrosinase-inhibiting activity through the skin in controlled, relatively large effective amounts over a prolonged period.

Further, in a first embodiment, the present invention provides a patch for percutaneous administration of such skin-whitening materials, which comprises a covering layer, a reservoir-adhesive layer and a detachable protective layer.

In a second embodiment, the present invention provides a patch for percutaneous administration of such skin-whitening materials, which comprises a covering layer, a reservoir, a release rate controlling membrane, an adhesive layer and a detachable protective layer.

The invention is further illustrated in the following Figures:

Fig. 1 is a cross-sectional view of an embodiment of patches (metrix type) according to the invention;

Fig. 2 is a cross-sectional view of another embodiment of patches (pouch type) according to the invention; and

Fig. 3 is a plot of ascorbic acid flux through skin in guinea pig for the patch of Example 1 (open circles) and for that of Example 2 (closed circles).

The present invention provides a new formulation form of skin-whitening materials. According to the invention, patches for percutaneous administration of one or more skin-whitening materials are provided.

The term "skin-whitening materials" as employed herein means compounds exhibiting melanin pigment formation-inhibiting ability via various mechanisms and which may be employed in cosmetics. Particularly, they may be selected from the group consisting of ascorbic acid and its derivatives. kojic acid and its derivatives, glycose amines, hydroquinone and its derivatives,

compounds having a thiol group, butylhydroxy toluene and butylhydroxy anisone. These compounds all have tyrosinase inhibiting activity.

The patches according to the present invention can improve the stability of active compounds against oxidation by oxygen or air by protecting them from the surrounding air or moisture.

The patches for transdermal permeation of skin-whitening materials of the present invention permit high local concentration of the materials so that it is possible to attain a satisfactory skin-whitening effect.

Further they cause no irritation to skin when applied to skin.

One preferred embodiment (matrix type) of patches according to the invention as shown in Fig. 1 comprises a covering layer (1), a reservoir-adhesive layer (2) containing active compounds, hydrophobic medicinal adhesives, permeation enhances, stabilizers, solubilizers, and skin irritation lenitives and a detachable protective layer (6).

The covering layer (1) is suitably made from a material or combination of materials that is substantially impermeable to water, air and the components of reservoir-adhesive layer (2). For example, the layer (1) is an aluminum-coated polyethylene terephtalate film or a film made from polymers such as ethylene vinylacetate, polypropylene, polyethylene, polyurethane or polyvinyl chloride. The covering layer (1) serves as a protective cover for the patch,

keeps the components of reservoir-adhesive layer (2) from escaping from the patch and fulfils a structural support function.

The detachable protective layer (6) is peeled away from the patch just prior to use. The layer (6) is suitably made from strippable and composition(2)-impermeable materials, such as silicone- or fluorine-coated polyester film or paper, or polyethylene terephtalate film.

The reservoir composition preferably comprises, based on the total weight of the composition, from 0.1 to 30% of one or more skin-whitening materials, from 8 to 99.68% of one or more medicinal hydrophobic adhesives, from 0.1 to 30% of one or more permeation enhancers, from 0.01 to 2% of one or more stabilizers, suitably weak acids, from 0.1 to 20% of one or more solubilizers and from 0.01 to 10% of a skin irritation lenitive.

The skin-whitening materials which have a melanin pigment formation-inhibiting activity may include, but not intended to be limited thereto, ascorbic acid or its derivatives such as ascorbic monopalmitate, ascorbic dipalmitate, ascorbic stearate, ascorbic monoethyl hexanoate, ascorbic diethyl hexanoate, ascorbic monooctanoate, ascorbic dioctanoate, ascorbic monoisostearate, ascorbic diisostearate, magnesium ascorbyl phosphate and sodium ascorbate; kojic acid and its derivatives with an alkyl group having 5 to 20 carbon atoms; glycose amines such as glucose amine, galactose amine and mannose amine; hydroquinone or its derivatives such as hydroquinone glycosides and hydroquinone benzyl ethers; compounds having a -SH group such as glutathiones and cysteins; butylhydroxy toluene (BHT); butylhydroxy anisone; propyl galate;

methionine; or lecithin. These skin-whitening materials may be employed alone or as mixtures thereof. The amount of skin-whitening material to be incorporated varies from 0.1 to 30% by weight, preferably 1.0 to 30% by weight.

The permeation enhancers which may be employed for enhancing the permeation of the skin-whitening materials through the skin may include, but not intended to be limited thereto, dimethyl sulfoxide, dodecyl sulfoxide, monomethyl acetamide, dimethyl acetamide, N-hydroxy ethyl lactide, higher fatty acid ester, salicylic acid, sorbitol, polyoxyethylene sorbitan fatty acid ester, sorbitan fatty acid ester, pyrrolidone derivatives, butylene glycolethyl ether, dodecylpyrrolidone, urea, glycerin, squalene, squalane, acetylated lanoline, cetyl laurate, olive oils, castor oil, lauric acid, oleic acid, lauryl alcohol, oleyl alcohol, ethoxystearyl alcohol, liquid paraffin, vaseline (petroleum jelly), 1-menthol, camphor, glycerin fatty acid ester, fatty acid mono- (or di-) ethanolamine, ethyleneglycol monoethyl ether, polyoxyethylene alkyl ether, polyoxyethylene alkyl ester, polyoxypropylene alkyl ether, propyleneglycol mono- (or di-) alkyl ester and the like. Further, the present invention advantageously employs a fatty acid ester such as glycerin monooleate, glycerin dioleate or propyleneglycol monooleate, a fatty acid ester with from 2 to 20 moles of ethylene oxide, a sorbitan fatty acid ester or a sorbitan fatty acid ester with from 10 to 100 moles of ethylene oxide to improve absorption of skin-whitening materials onto the skin.

Moreover, in the practice of the present invention, a skin irritation lenitive such as glycerin or bisabolol is advantageously employed to reduce skin-irritation caused by the components of the patch.

The stabilizers for skin-whitening materials may be incorporated in a small amount to the patch and may include, not intended to be limited thereto, a weak acid such as citric acid, succinic acid, oxalic acid or formic acid.

The solubilizer, which can be employed for increasing solubility of skin-whitening materials and promoting the delivery of skin-whitening materials, may include, but not intended to be limited thereto, 1,3-butyleneglycol, propylene glycol, glycerin, a polyol such as polyethylene glycol or polyethylene glycol-propylene glycol copolymer, and an alcohol such as ethanol, methanol, isopropanol or butanol.

According to the invention, one or more medicinal hydrophobic adhesives may be incorporated into reservoir-adhesive layer in order to tack the patch and prevent skin-whitening material from being contacted with moisture. The medicinal hydrophobic adhesives may include, but not intended to be limited thereto, acrylic, silicone, polyisobutylene, and synthetic or natural rubbery resin adhesives. The acrylic adhesives may include a (meth)acrylic alkyl ester polymer in which alkyl group has 4 to 18 carbon atoms and a copolymer of (meth)acrylic alkyl ester with other functional monomers.

Examples (meth)acrylic alkyl ester polymer may include butyl acrylate, isobutyl acrylate, hexyl acrylate, octyl

acrylate, 2-ethylhexyl acrylate, isooctyl acrylate, decyl acrylate, isodecyl acrylate, lauryl acrylate, stearyl acrylate, methyl methacrylate, ethyl methacrylate, butyl methacrylate, isobutyl methacrylate, 2-ethylhexyl methacrylate, isooctyl methacrylate, decyl methacrylate, isodecyl methacrylate, lauryl methacrylate, stearyl methacrylate and the like.

The functional monomers may include, for example, a monomer with hydroxyl group such as 2-hydroxyethyl (meth)acrylate and hydroxypropyl (meth)acrylate; a monomer with carboxyl group such as a α- or ß- unsaturated carboxylic acid (e.g., acrylic acid, methacrylic acid), maleic monoalkyl ester (e.q., butyl maleate), maleic acid, fumaric acid and crotonic acid; a monomer with amide group such as alkyl (meth)acrylamide (e.g., acrylamide, dimethyl acrylamide, diethyl acrylamide), alkylethylmethylol (meth)acrylamide (e.g., butoxymethyl acrylamide, ethoxymethyl acrylamide), diacetone acrylamide, and vinylpyrrolidone; a monomer with amino group such as dimethyl aminoacrylate. Further, monomers such as vinyl acetate, styrene, α-methyl styrene, vinyl chloride, acrylonitrile, ethylene, butadiene and propylene may be employed to obtain copolymer of (meth)acrylic alkyl ester.

The acrylic adhesives advantageously contain more than 50% by weight of (meth)acrylic alkyl ester.

The rubbery resin adhesives may include, for example, natural rubber, polyisoprene, polyisobutylene. polyvinyl ether, polyurethane, polybutadiene, styrene-butadiene

copolymer, styrene-isoprene copolymer, styrene-isoprene-butylene block copolymer and the like.

The silicone resin adhesives is advantageously a silicate rubber (60% by weight) cross-linked with polydimethyl siloxane resin (40% by weight).

The adhesives, if necessary, may contain auxiliary agents, for example a tackifier such as a rosin resin, a polyterpene resin, a coumarone-indene resin, a petroleum resin and a terpene phenol resin; a plasticizer such as liquid polybutene, a mineral oil, lanoline, liquid isoprene and liquid polyacrylate; a filler; an aging retarding agent; and the like.

The medicinal hydrophobic adhesives may be incorporated into reservoir-adhesive layer(2) in an amount varying from 8 to 99.68% by weight.

The matrix-type patches according to the invention as shown in Fig. 1 may be fabricated as follows:

A reservoir composition is prepared by dispersing in an organic solvent such as hexane, ethyl acetate or chloroform from 0.1 to 30% by weight of one or more skin-whitening materials, from 0.1 to 30% by weight of one or more permeation enhancers, from 0.01 to 2% by weight of one or more stabilizers, from 0.01 to 10% by weight of one or more lenitives and from 0.1 to 20% by weight of one or more solubilizers, adding from 8 to 99.68% by weight of one or more medicinal hydrophobic adhesives thereto, stirring the mixture for more than 1 hour until a homogenous blend is obtained and allowing to stand at room temperature to remove foams. The

resulting mixture is evenly applied on a silicone- or fluorine-coated paper or a polyethylene terephtalate film (6) with an applicator to a thickness from 10 to 200μm. Then the paper or film is allowed to stand at room temperature for more than 1 hour to evaporate solvent. If necessary, the paper or film may be further dried in a hot air dryer (80°C) for about 10 minutes.

After completion of solvent evaporation, a covering layer (1) selected from, for example, aluminum-coated polyethylene terephtalate, ethylene vinyl acetate or polypropylene film is sealed by adhesion or fusion onto the reservoir composition-loaded film so obtained. Then, the sealed laminate is aged in an incubator (37°C) for 12 to 24 hours and fabricated into patches having a surface area to be attached to skin of varying sizes from 0.1 to 500cm^2.

Another preferred embodiment of patches according to the invention is in the form of a laminated pouch as shown in Fig. 2, which is formed from a covering layer(1) bonded at its periphery to, and spaced apart at its central portion from, a release rate controlling membrane(4) which is coated with an adhesive(5) provided with a detachable protective layer(6). The pouch is filled with a composition(3) of skin-whitening materials.

The covering layer(1) and detachable protective layer(6) are made from the same materials as described above for the patch shown in Fig. 1. The adhesive(5) may be selected from those described above for the reservoir-adhesive layer(2) of the patch shown in Fig. 1.

The composition(3) comprises based on the total weight of the composition from 0.1 to 30% by weight of one or more skin-whitening materials, from 0.1 to 30% by weight of one or more permeation enhancers, from 0.01 to 2% by weight of one or more stabilizers, from 0.01 to 10% by weight of one or more lenitives and from 28 to 99.78% by weight of solubilizers.

The release rate controlling membrane(4) is a microporous membrane that controls the rate at which the skin-whitening materials and permeation enhancers are released from the reservoir(3). The membrane may be formed from polymers such as polypropylene, polycarbonate, polyvinylchloride, and ethylene vinyl acetate.

This embodiment of patch shown in Fig. 2 can be particularly advantageously employed where a controlled transdermal permeation of relatively large effective amounts of skin-whitening materials is required.

The laminate pouch-type patches according to invention as shown in Fig. 2 may be fabricated as follows:

One or more adhesives(5) selected from those described above are dissolved in a suitable organic solvent and the solution so obtained is evenly applied with an applicator onto a paper coated with silicone or fluorine or a polyethylene terephtalate film(6) to a thickness from 10 to 200μm. Then the paper or film is allowed to stand at room temperature for more than 1 hour to evaporate solvent. If necessary, the paper or film may be further dried in a hot air dryer(80°C) for about 10 minutes.

After completion of solvent evaporation, the paper or

film is sealed with a microporous membrane (4).

Besides a reservoir composition (3) is prepared by mixing skin-whitening materials, permeation enhancers, stabilizers, lenitives and solubilizers and stirring the mixture until a homogenous blend is obtained. Then, the composition is pouched between the covering layer(1) and the laminate composed of microporous membrane (4), adhesive layer (5) and a detachable protective layer (6) and the layers are peripherally thermosealed.

The laminates can be fabricated into patches having a surface area to be attached to skin of varying sizes from 0.1 to 500cm^2. The permeability of skin-whitening materials through human skin is preferably in the range of about 0.01 to 50$\mu g/cm^2/hr$.

The present invention will be embodied by way of the following examples. However, these examples are provided for the illustration purpose only and should not be construed as limiting the scope of the invention, which is properly delineated in the accompanying claims.

Examples 1 to 5

(% by weight)

Composition	Ex 1	Ex 2	Ex 3	Ex 4	Ex 5
Acryl-vinyl acetate copolymer	76	76	76	76	75
Ascorbic acid	3	3			1
Ascorbic monopalmitate			3	3	3
Propylene glycol monooleate	20		20		20
Polyoxyethylene(20) sorbitan oleate		20		20	
Alpha-bisabolol	1	1	1	1	1

The above materials are mixed together and stirred until a homogenous blend is obtained. Then the resulting mixture is applied with an applicator onto a silicone-coated paper to a thickness of about 50μm. Then, the paper is allowed to stand at room temperature for more than 1 hour to evaporate solvent. The composition-loaded paper is sealed by fusion onto an aluminum-coated polyethylene terephtalate film. The laminate is aged in an incubator(37°C) for 12 to 24 hours and fabricated into about 20cm^2 matrix-type patches.

Examples 6 to 9

(% by weight)

Composition	Ex 6	Ex 7	Ex 8	Ex 9
Silicone resin	76	76	76	76
Ascorbic dipalmitate	3	3		
Ascorbic stearate			3	3
Glycerin monooleate	20		20	
Polyoxyethylene(3) lauryl ether		20		20
Alpha bisabolol	1	1	1	1

By following the procedure in Examples 1 to 5, about $30cm^2$ matrix-type patches are fabricated.

Examples 10 to 13

(% by weight)

Composition	Ex 10	Ex 11	Ex 12	Ex 13
Polyvinyl ether polymer	76	76	76	76
Magnesium ascorbyl phosphate	3	3		
Kojic acid			3	3
Propyleneglycol monolaurate	20		20	
N-pyrrolidone		20		20
Alpha-bisabolol	1	1	1	1

By following the procedure in Examples 1 to 5 except that a fluorine-coated polyester film and a polyethylene film are employed instead of silicone-coated paper and aluminum-coated polyethylene terephtalate film, respectively, about $30cm^2$ matrix-type patches are fabricated.

Examples 14 to 17

(% by weight)

Composition	Ex 14	Ex 15	Ex 16	Ex 17
Natural rubbery resin	76	76	76	76
Glucose amine	3	3		
Albutine			3	3
Dodecyl sulfoxide	20		20	
Oleyl alcohol		20		20
Alpha-bisabolol	1	1	1	1

By following the procedure in Examples 10 to 13, about $30cm^2$ matrix-type patches are fabricated.

Examples 18 to 21

(% by weight)

Composition	Ex 18	Ex 19	Ex 20	Ex 21
Rubbery resin	76	76	76	76
Ascorbic acid	1	1		
Ascorbic monopalmitate	1		1	
Ascorbic dipalmitate	1		1	
Kojic acid		1	1	1
Glucose amine		1		1
Hydroquinone				1
Polyethyleneglycol-polypropyleneglycol copolymer	5	5	5	5
N-pyrrolidone	5	5	5	5
Glycerin monooleate	5	5	5	5
Polyoxyethylene(3) lauryl ether	5	5	5	5
Citric acid	0.1	0.1	0.1	0.1
Alpha-bisabolol	0.9	0.9	0.9	0.9

By following the procedure in Examples 1 to 5, about 20cm^2 matrix-type patches are fabricated.

Examples 22 to 25

(% by weight)

Composition	Ex 22	Ex 23	Ex 24	Ex 25
Ascorbic acid	3	3		
Ascorbyl monopalmitate			3	3
Oleic acid	10		10	
Polyoxyethylene(3) oleyl ether		10		10
Citric acid	0.1	0.1	0.1	0.1
Alpha-bisabolol	1	1	1	1

The above materials are mixed together and stirred until a homogenous blend is obtained.

Besides, butyl acrylate and decyl methacrylate are dissolved in hexane and the solution is applied with an applicator onto a siliconized paper, and the paper is allowed to stand at room temperature for more than 1 hour and dried in a hot air dryer(80°C) for about 10 minutes. The adhesive layer-detachable protective layer combination is then laminated to one face of a 25 micron thick microporous polypropylene membrane.

The composition obtained above is pouched by using a form-fill-seal pouching machine between the aluminized polyethylene terephtalate covering film and the above microporous membrane-adhesive layer-detachable protective layer laminate and the layers are peripherally thermosealed. About 20cm^2 pouch-type patches are cut from the resulting 5-layer laminate.

Experimental Example 1 : Transdermal Permeation Rate

The abdominal hair was removed from a guinea pig weighing about 350g using a hair clipper a section of the hairless abdominal skin was excised and stored at a refrigerator (below -20°C), which will be thawed for use.

The skin specimen was placed in the middle of the ranz-type diffusion cell, the corneous side of the skin looking upward. The receptor was charged with an aqueous 50% by volume glycerin solution. 2.5cm^2 circular, disc-shaped patches of Examples 1 to 9, and 18 to 21 were applied to the skin specimen while stirring the receptor's solution at 600

rpm at 30°C. Besides, conventional cosmetic compositions(skin lotions) containing 3% ascorbic acid, 3% ascorbic monopalmitate, 3% ascorbic dipalmitate, 3% ascorbic stearate or 3% ascorbic monoethyl hexanoate as controls were applied to the skin specimen.

The receptor solutions were sampled at 1 hour intervals and analyzed for concentrations of skin-whitening materials using high pressure liquid chromatography(HPLC).

Transdermal permeation rates were calculated from the concentrations and are shown in Table 1.

Table 1

Test sample	Transdermal permeation rate ($\mu g/cm^2/hr$)
3% Ascorbic acid-containing composition	1.3
3% Ascorbyl monopalmitate-containing composition	2.1
3% Ascorbyl dipalmitate-containing composition	1.8
3% Ascorbyl stearate-containing composition	1.0
3% Ascorbyl monoethylhexanoate-containing composition	0.7
Patch in Example 1	6.7
Patch in Example 2	7.3
Patch in Example 3	8.3
Patch in Example 4	8.2
Patch in Example 5	8.6
Patch in Example 6	7.8
Patch in Example 7	8.1

Patch in Example 8	7.2
Patch in Example 9	7.5
Patch in Example 18	9.3
Patch in Example 19	9.1
Patch in Example 20	8.8
Patch in Example 21	8.9

As shown in Table 1, the patches according to the invention allow permeation of larger amount of skin-whitening material when compared with the conventional cosmetic compositions for whitening skin.

Experimental Example 2 : Pigment Deposition-Inhibiting ability

20 healthy volunteers were covered with aluminum foil at their lower arms except a $2x2cm^2$ section to be UV-irradiated. The section was well washed with aqueous 70% isopropyl solution and irradiated using L 20S BLB and L 20S E-30 lamps(Toshiba, Japan) simultaneously, which are located at 10cm distance from the arm, at $0.8\text{-}10^7$ erg/cm^3 once a day. The UV-irradiation was effected for three consecutive days.

After irradiation, the section was applied with the test cosmetic compositions in Experimental Example 1 twice a day or the patches in Experimental Example 1 once a day. One month later, the test section was evaluated for pigment deposition-inhibiting ability of test samples.

The number of subjects experiencing significant, good or no pigment inhibition was counted and are shown in Table 2.

Table 2

Test samples	Number of subjects experiencing significant pigment deposition inhibition	Good pigment deposition inhibition	No pigment deposition inhibition
3% Ascorbic acid-containing composition	0	2	18
3% Ascorbyl monopalmitate-containing composition	0	4	16
3% Ascorbyl dipalmitate-containing composition	0	3	17
3% Ascorbyl stearate-containing composition	0	4	16
3% Ascorbyl monoethylhexanoate-containing composition	0	4	16
Patch in Example 1	5	12	3
Patch in Example 2	4	11	5
Patch in Example 3	8	11	1
Patch in Example 4	7	13	0
Patch in Example 5	12	8	0
Patch in Example 6	5	13	2
Patch in Example 7	5	12	3
Patch in Example 8	6	12	2
Patch in Example 9	6	11	3
Patch in Example 18	10	9	1
Patch in Example 19	8	12	0
Patch in Example 20	9	10	1
Patch in Example 21	13	7	0
Patch in Example 22	7	13	0
Patch in Example 23	7	13	0

Patch in Example 24	10	10	0
Patch in Example 25	7	13	0

As shown in Table 2, the patches of the invention exhibit far more efficient pigment deposition-inhibiting activity than the conventional cosmetic compositions do.

Experimental Example 3 : Stability of Active Compound

The cosmetic compositions and patches shown in Table 3 were stored at an incubator of 50°C for 2 months and extracted for their active compounds with methanol. The active compounds were determined for their titer by high pressure liquid chromatography (HPLC) and the results are shown in Table 3.

Table 3

Test sample	Titer(%)
3% Ascorbic acid-containing composition	12
3% Ascorbyl monopalmitate-containing composition	58
3% Ascorbyl dipalmitate-containing composition	67
3% Ascorbyl stearate-containing composition	59
3% Ascorbyl monoethylhexanoate-containing composition	15
Patch in Example 1	98
Patch in Example 2	97
Patch in Example 3	99
Patch in Example 4	99

Patch in Example 5	98
Patch in Example 6	98
Patch in Example 7	99
Patch in Example 8	99
Patch in Example 9	99
Patch in Example 18	97
Patch in Example 19	97
Patch in Example 20	98
Patch in Example 21	97

As shown in Table 3, the patches according to the invention retain higher titer even when after storing 2 months at 50°C than the conventional cosmetic compositions do, indicating that the patches of the invention permit the active compounds therein remain stable for a long time.

Experimental Example 4 : Skin Primary Irritation Test

20 healthy volunteers were applied 2cm^2 circular, disc shaped patches shown in Table 4 on their lower arm one patch/day. Besides, conventional cosmetic compositions shown in Table 4 were applied onto the lower arm of volunteers twice a day and the portion applied by the composition was covered with a metal cap.

1-, 3- or 7- day later, the skin irritation was evaluated in accordance with the following standards:

Score	Level of irritation
0	No irritation
1	Minimum irritation
2	Weak irritation (erythema)
3	Severe irritation (erythema, edema)
4	Extremely severe irritation(erythema, edema)

Table 4

Test sample	Skin irritation(%) after 1 day	3 day	7 day
3% Ascorbic acid-containing composition	0.5	0.5	0.5
3% Ascorbyl monopalmitate-containing composition	0.5	0.5	0.8
3% Ascorbyl dipalmitate-containing composition	1.0	0.8	1.0
3% Ascorbyl stearate-containing composition	0.8	1.0	0.8
3% Ascorbyl monoethylhexanoate-containing composition	1.0	1.0	0.8
Patch in Example 1	0.8	0.8	1.0
Patch in Example 2	0.5	0.8	0.8
Patch in Example 3	1.0	0.8	1.0
Patch in Example 4	0.8	0.8	1.0
Patch in Example 5	1.0	0.8	0.8
Patch in Example 6	0.5	0.5	1.0
Patch in Example 7	0.8	1.0	1.0
Patch in Example 8	1.0	1.3	1.3
Patch in Example 9	0.8	1.0	1.3

Patch in Example 18	1.0	1.3	1.3
Patch in Example 19	0.8	1.0	1.3
Patch in Example 20	1.0	1.0	1.3
Patch in Example 21	0.8	1.3	1.0

As shown in Table 4, the patches of the invention comprising alpha-bisabolol as a lenitive cause as weak skin irritation as the conventional cosmetic composition. Thus, the patches according to the invention may be safely applied on skin in order to whiten the skin.

CLAIMS

1. A patch for percutaneous administration which comprises one or more skin-whitening materials as an active component, the skin-whitening materials having tyrosinase-inhibiting activity.

2. A patch according to claim 1, wherein said patch is composed of a covering layer, a reservoir-adhesive layer and a detachable protective layer.

3. A patch according to claim 1, wherein said patch is composed of a covering layer, a reservoir, a release rate controlling membrane, an adhesive layer and a detachable protective layer.

4. A patch according to claim 2, wherein the reservoir-adhesive layer comprises based on the total weight of the composition from 0.1 to 30% of one or more skin-whitening materials selected from the group consisting of ascorbic acid or its derivatives such as ascorbic monopalmitate, ascorbic dipalmitate, ascorbic stearate, ascorbic monoethyl hexanoate, ascorbic diethyl hexanoate, ascorbic monooctanoate, ascorbic dioctanoate, ascorbic monoisostearate, ascorbic diisostearate, magnesium ascorbyl phosphate and sodium ascorbate; kojic acid and its derivatives with an alkyl group having 5 to 20 carbon atoms; glycose amines such as glucose amine, galactose amine and mannose amine; hydroquinone or its derivatives such as hydroquinone glycosides and hydroquinone benzyl ethers; compounds having a -SH group such as glutathiones and cysteins; butylhydroxy toluene (BHT); butylhydroxy anisone; propyl galate; methionine; and lecithin; from 0.1 to 30% of one or more permeation enhancers selected from the group consisting of dimethyl sulfoxide, dodecyl sulfoxide,

monomethyl acetamide, dimethyl acetamide, N-hydroxy ethyl lactide, polyoxethylene (E.O. = 2-20) fatty ether, higher fatty acid ester for example, glycerin monooleate, glycerin dioleate or propyleneglycol monooleate, salicyclic acid, sorbitol, polyoxyethylene (E.O = 10-100) sorbitan fatty acid ester, sorbitan fatty acid ester, pyrrolidone derivatives, butylene glycolethyl ether, dodecylpyrrolidone, urea, glycerin, squalene, squalane, acetylated lanolin, cetyl laurate, olive oils, castor oil, lauric acid, oleic acid, lauryl alcohol, oleyl alcohol, ethoxystearyl alcohol, liquid paraffin, vaseline (petroleum jelly), 1-menthol, camphor, glycerin fatty acid ester, fatty acid mono-(or di-)ethanolamine, ethyleneglycol monoethyl ether, polyoxyethylene alkyl ether, polyoxyethylene alkyl ester, polyoxypropylene alkyl ether, and propyleneylycol mono-(or di-)alkyl ester; from 0.01 to 2% of one or more stabilizers selected from the group consisting of succinic acid, citric acid, oxalic acid and formic acid; from 0.1 to 20% of one or more solubilizers selected from the group consisting, 1,3-butylene glycol, propylene glycol, glycerin, polyethylene glycol, polyethyleneglycol-propyleneglycol copolymer, ethanol, isopropanol, methanol and butanol; from 0.01 to 10% of one or more lenitives selected from the group consisting of glycerin and alpha-bisalbolol; and from 8 to 99.68% of one or more medicinal hydrophobic adhesives selected from the group consisting of acrylic, silicone resin, polyisobutylene, natural or synthetic rubbery resin and polyisobutylene adhesives.

5. A patch according to claim 3, wherein the reservoir layer comprises based on the total weight of the composition from 0.1 to 30% of one or more skin-whitening materials selected from the group consisting of ascorbic acid or its derivatives such as ascorbic monopalmitate, ascorbic dipalmitate, ascorbic

stearate, ascorbic monoethyl hexanoate, ascorbic diethyl hexanoate, ascorbic monooctanoate, ascorbic dioctanoate, ascorbic monoisostearate, ascorbic diisostearate, magnesium ascorbyl phosphate and sodium ascorbate; kojic acid and its derivatives with an alkyl group having 5 to 20 carbon atoms; glycose amines such as glucose amine, galactose amine and mannose amine; hydroquinone or its derivatives such as hydroquinone glycosides and hydroquinone benzyl ethers; compounds having a -SH group such as glutathiones and cysteins; butylhydroxy toluene (BHT); butylhydroxy anisone; propyl galate; methionine; and lecithin; from 0.1 to 30% of one or more permeation enhancers selected from the group consisting of dimethyl sulfoxide, dodecyl sulfoxide, monomethyl acetamide, dimethyl acetamide, N-hydroxy ethyl lactide, polyoxyethylene (E.O. = 2-20) fatty ether, fatty acid ester for example, glycerin monooleate, glycerin dioleate, or propyleneglycol monooleate, salicylic acid, sorbitol, polyoxyethylene (E.O. = 10-100) sorbitan fatty acid ester, sorbitan fatty acid ester, pyrrolidone derivatives, butylene glycolethyl ether, dodecylpyrrolidone, urea, glycerin, squalene, squalane, acetylated lanolin, cetyl laurate, olive oils, castor oil, lauric acid, oleic acid, lauryl alcohol, oleyl alcohol, ethoxystearyl alcohol, liquid paraffin, vaseline (petroleum jelly), l-menthol, camphor, glycerin fatty acid ester, fatty acid mono-(or di-) ethanolamine, ethyleneglycol monoethyl ether, polyoxyethylene alkyl ether, polyoxyethylene alkyl ester, polyoxypropylene alkyl ether, and propyleneglycol mono-(or di-) alkyl ester; from 0.01 to 2% of one or more stabilizers selected from the group consisting of succinic acid, citric acid, oxalic acid and formic acid; from 28 to 99.78% of one or more solubilizers selected from the group consisting 1,3-butylene glycol, propylene glycol, glycerin, polyethylene glycol, polyethylene glycol-propylene glycol copolymer, ethanol, isopropanol, methanol

and butanol; and from 0.01 to 10% of one or more lenitives selected from the group consisting of glycerin and alpha-bisabolol; and the adhesive layer is formed from one or more medicinal hydrophobic adhesives selected from the group consisting of acrylic, silicone resin, natural or synthetic rubbery resin and polyisobutylene adhesives.

6. A patch according to claim 4 or 5, wherein the acrylic adhesive is a (meth)acrylic C_{4-18} alkyl ester polymer or a copolymer of (meth)acrylic C_{4-18} alkyl ester with other functional monomers.

7. A patch according to claim 6, wherein the (meth) acrylic C_{4-18} alkyl ester polymer is butyl acrylate, isobutyl acrylate, hexyl acrylate, octyl acrylate, 2-ethylhexyl acrylate, isooctyl acrylate, decyl acrylate, isodecyl acrylate, lauryl acrylate, stearyl acrylate, methyl methacrylate, ethyl methacrylate, butyl methacrylate, isobutyl methacrylate, 2-ethylhexyl methacrylate, isooctyl methacrylate, decyl methacrylate, isodecyl methacrylate, lauryl methacrylate, or stearyl methacrylate; and the other functional monomer is a monomer with hydroxyl group such as 2-hydroxyethyl (meth)acrylate and hydroxypropyl (meth)acrylate; a monomer with carboxyl group such as a α- or β- unsaturated carboxylic acid (e.g., acrylic acid, methacrylic acid), maleic monoalkyl ester (e.g., butyl maleate), maleic acid, fumaric acid and crotonic acid; a monomer with amide group such as alkyl (meth)acrylamide (e.g., acrylamide, dimethylacrylamide, diethylacrylamide), alkylethylmethylol (meth)acrylamide (e.g., butoxymethylacrylamide, ethoxymethylacrylamide), diacetone acrylamide, and vinylpyrrolidone; a monomer with amino group such as dimethyl aminoacrylate; vinyl acetate; styrene; α-methyl styrene; vinyl chloride, acrylonitrile; ethylene; butadiene or propylene.

8. A patch according to claim 4 or 5, wherein the rubbery resin adhesive is natural rubber, polyisoprene, polyisobutylene, polyvinyl ether, polyurethane, polybutadiene, styrene-butadiene copolymer, styrene-isoprene copolymer or styrene-isoprene-butylene block copolymer; and the silicone resin adhesive is a silicate rubber (60% by weight) cross-linked with polydimethyl siloxane resin (40% by weight).

9. A patch according to claim 3, wherein the release rate controlling membrane is a microporous membrane formed from polypropylene, polyethylene, ethylene-vinyl acetate copolymer or polyvinyl pyrrolidone.

10. A patch according to claim 2 or 3, wherein the covering layer is formed from a polyethylene terephtalate film coated with aluminum, or ethylene vinyl acetate, polypropylene, polyethylene, polyurethane or polyvinylchloride film.

11. A patch according to claim 2 or 3, wherein the detachable protective layer is formed from a paper or polyester film coated with silicone or fluorine, or a polyethylene terephtalate film.

12. A patch acceding to any preceding claim, wherein which is designed to have a permeability of skin-whitening materials from 0.01 to 50$\mu g/cm^2/hr$.

13. A patch according to any preceding claim substantially as herein described with reference to the Examples.

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Relevant Technical fields

(i) UK Cl (Edition L) A5B (BLG, BFH)

(ii) Int Cl (Edition 5) A61K

Search Examiner

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Databases (see over)

(i) UK Patent Office

(ii) ONLINE DATABASES: WPI, CLAIMS, CAS ONLINE

Date of Search

18 MAY 1993

Documents considered relevant following a search in respect of claims 1-13

Category (see over)	Identity of document and relevant passages		Relevant to claim(s)
XY	EP 0253901 A1	(TEIJIN) - see Figures page 9 lines 24 etc. Pages 18 and 19 referring to Vitamin C and glutathione	X - 1 Y - 1-4
Y	EP 0227252 A2	(ALZA) (US 4698062) see abstract. Examples. Claims Referred to in application	1-4
Y	EP 0200562 A2	(ALZA) (& US 4615699) - see abstract. Claim 1. Examples. Referred to in application	1-4
Y	US 4738670	(BAYER) - see abstract. Claims 1-5. Referred to in application.	1-4

Category	Identity of document and relevant passages	Relevant to claim(s)

Categories of documents

X: Document indicating lack of novelty or of inventive step.

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A: Document indicating technological background and/or state of the art.

P: Document published on or after the declared priority date but before the filing date of the present application.

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